1: Cell Regul 1991 Feb;2(2):165-79 Related Articles, Links

# The two mammalian mitochondrial stress proteins, grp 75 and hsp 58, transiently interact with newly synthesized mitochondrial proteins.

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In mammalian cells, two of the so-called heat shock (hsp) or stress proteins are components of the mitochondria. One of these, hsp 58, is a member of the bacterial GroEL family, whereas the other, glucose-regulated protein (grp) 75, represents a member of the hsp 70 family of stress proteins. Owing to previous studies implicating a role for both the hsp 70 and GroEL families in facilitating protein maturation events, we used the method of native immunoprecipitation to examine whether hsp 58 and grp 75 might interact with other proteins of the mitochondria. In cells pulse-labeled with [35S]-methionine, a significant number of newly synthesized mitochondrial proteins co-precipitated with either hsp 58 or grp 75. Such interactions appeared transient. For example, providing the pulse-labeled cells a subsequent chase period in the absence of radiolabel resulted in a reduction of co-precipitating proteins. If the pulse-chase labeling experiments were performed in the presence of an amino acid analogue, somewhat different results were obtained. Specifically, although many of the newly synthesized and analogue-containing proteins again were observed to co-precipitate with grp 75, the interactions did not appear transient, but instead were stable. Under steady-state labeling conditions, we also observed a portion of hsp 58 and grp 75 in an apparent complex with one another. On addition of ATP, the complex was dissociated. Accompanying this dissociation was the concomitant autophosphorylation of grp 75. On the basis of these observations, as well as previous studies examining the structure/function of the hsp 70 and GroEL proteins, we suspect that both hsp 58 and grp 75 interact with and facilitate the folding and assembly of proteins as they enter into the mitochondria.

PMID: 1677814 [PubMed - indexed for MEDLINE]

1: Biochem Biophys Res Commun 1992 Dec 15;189 (2):1150-6



# Dissociation of complexes between 70 kDa stress proteins and presecretory proteins is facilitated by a cytosolic factor.

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Members of the 70 kDa stress protein family were shown previously to facilitate the posttranslational translocation of presecretory proteins into the endoplasmic reticulum and protein precursors into mitochondria. To identify proteins that interact with 70 kDa stress proteins during the early steps of posttranslational translocation, polyclonal antibodies were raised against purified yeast cytosolic stress proteins. They were used to immunoprecipitate complexes between 70 kDa stress proteins and a radiolabeled presecretory protein, prepro-alpha-factor, that was translated in vitro. Complexes between prepro-alpha-factor and 70 kDa stress proteins were stable, but could be dissociated in the presence of ATP and crude cytosolic extracts from yeast. These results are consistent with the idea that 70 kDa stress proteins act as molecular chaperones in translocation by binding to precursor proteins before or during their passage across membranes.

PMID: 1472025 [PubMed - indexed for MEDLINE]

Comment in:

- Lancet. 1994 Mar 19;343(8899):684-5.
- Lancet. 1994 May 7;343(8906):1168-9.

## Peptide therapy for diabetes in NOD mice.

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NOD mice spontaneously develop autoimmune diabetes that mimics insulin-dependent diabetes mellitus (IDDM) in man. A peptide of the 60 kDa heat shock protein (hsp60), designated p277, can serve as a target for diabetogenic T-cell clones, and diabetes was prevented by using the p277 peptide to turn off anti-p277 immunity early in life. We report that the p277 peptide, administered once, can arrest the autoimmune process even after it is far advanced. Successful therapy was associated with down-regulation of the autoimmune process and regression of islet inflammation. Thus the immune system is responsive to manipulation by a specific signal even in the face of a virulent, full-blown autoimmune process.

PMID: 7907681 [PubMed - indexed for MEDLINE]

1: Eur J Immunol 1995 Oct;25(10):2851-7 Related Articles, Links

# Induction of diabetes in standard mice by immunization with the p277 peptide of a 60-kDa heat shock protein.

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We previously reported that immunity to the p277 peptide of the human 60-kDa heat shock protein (hsp60) was a causal factor in the diabetes of non-obese diabetic (NOD) mice, which are genetically prone to develop spontaneous autoimmune diabetes. The present study was done to test whether immunization with the p277 peptide could cause diabetes in standard strains of mice. We now report that a single administration of the p277 peptide conjugated to carrier molecules such as bovine serum albumin or ovalbumin can induce diabetes in C57BL/6 mice and in other strains not genetically prone to develop diabetes. The diabetes was marked by hyperglycemia, insulitis, insulin autoantibodies, glucose intolerance and low blood levels of insulin. The diabetes could be transferred to naive recipients by anti-p277 T cell lines. Similar to other experimentally induced autoimmune diseases, the autoimmune diabetes remitted spontaneously. After recovery, the mice were found to have acquired resistance to a second induction of diabetes. Susceptibility to induced diabetes in C57BL/6 mice was influenced by sex (males were much more susceptible than were females) and by class II genes in the major histocompatibility complex (B6.H-2bm12 mice with a mutation in the MHC-II molecule were relatively resistant). Other strains of mice susceptible to induced diabetes were C57BL/KSJ, C3HeB/FeJ, and NON/Lt. BALB/c and C3H/HeJ strains were relatively resistant. Immunization to p277-carrier conjugates could also induce transient hyperglycemia in young NOD mice, but upon recovery from the induced diabetes, the NOD mice were found to have acquired resistance to later development of spontaneous diabetes. Thus, T cell immunity to the p277 peptide can suffice to induce diabetes in standard mice, and a short bout of induced diabetes can affect the chronic process that would otherwise lead to spontaneous diabetes in diabetes-prone NOD mice.

PMID: 7589082 [PubMed - indexed for MEDLINE]